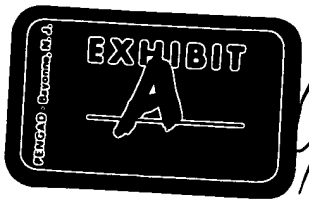

#17 Attach

MOLECULAR BIOLOGY OF THE CELL

Bruce Alberts • Dennis Bray
Julian Lewis • Martin Raff • Keith Roberts
James D. Watson

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"Long ago it became evident that the key to every biological problem must finally be sought in the cell, for every living organism is, or at sometime has been, a cell."

Edmund B. Wilson
The Cell in Development and Heredity
3rd edition, 1925, Macmillan, Inc.

Bruce Alberts received his Ph.D. from Harvard University and is currently a Professor in the Department of Biophysics and Biochemistry at the University of California Medical School in San Francisco. *Dennis Bray* received his Ph.D. from the Massachusetts Institute of Technology and is currently a Senior Scientist in the Medical Research Council Cell Biophysics Unit at King's College London. *Julian Lewis* received his D.Phil. from Oxford University and is currently a Lecturer in the Anatomy Department at King's College London. *Martin Raff* received his M.D. degree from McGill University and is currently a Professor in the Zoology Department at University College London. *Keith Roberts* received his Ph.D. from Cambridge University and is currently Head of the Department of Cell Biology at the John Innes Institute, Norwich. *James D. Watson* received his Ph.D. from the University of Indiana and is currently Director of the Cold Spring Harbor Laboratory. He is the author of *Molecular Biology of the Gene* and, with Francis Crick and Maurice Wilkins, won the Nobel Prize in Medicine and Physiology in 1962.

Cover photograph kindly provided by Michael Verderame and Robert Pollack of Columbia University. The fluorescein-phalloidin used to stain the actin cables was the generous gift of Drs. Theodor Wieland and A. Deboben of the Max Planck Institute, West Germany. The photograph is of a mouse fibroblast that had been transformed to anchorage-independent growth by the virus Simian Virus 40 (SV40) and subsequently selected for anchorage-dependent growth. This particular cell was stained for SV40 large T antigen (*red*) and fluorescein-phalloidin (*green*), which specifically stains F actin.

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Many of the newly formed capillaries will regress and disappear when the process of repair is complete.

Perhaps the most striking demonstration that tissues can produce signals for angiogenesis comes from studies on tumor growth. A tumor that grows as a solid mass remains small unless it is provided with capillaries: without a blood supply that extends into its interior, the tumor must rely on diffusion of nutrients from its exterior and so cannot enlarge beyond a diameter of a few millimeters. But if the tumor cells can induce the formation of a capillary network that invades the tumor mass, there need be no limit to the tumor's growth. There is good evidence that tumors capable of unlimited growth release a substance, called *tumor angiogenesis factor*, that acts on endothelial cells in just this way. A small sample of such tumor tissue implanted in the cornea will cause blood vessels to grow quickly toward the implant from the vascular margin of the cornea (Figure 16–19). It is possible that normal cells deprived of oxygen may attract a blood supply by secreting the same angiogenic factor.

The dependence of tumor cells on endothelial cells illustrates a theme to which we shall return at the end of this chapter. It shows that the problem of cancer must be considered not only in terms of the behavior of the cancer cell itself, but also in terms of its relationships with other cells in the body.

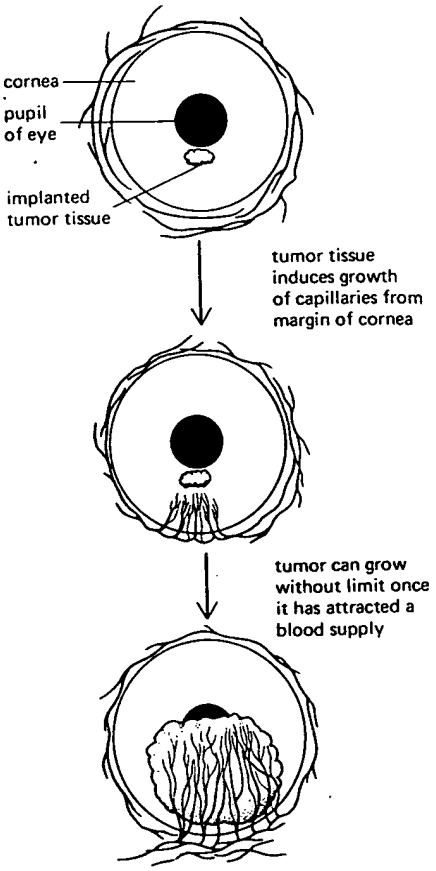

Figure 16–19 Tumor tissue implanted in the cornea releases a factor that causes the ingrowth of capillaries, supplying the tumor with blood-borne nutrients that allow it to grow. The ingrowth of capillaries is called angiogenesis.

Summary

Most populations of differentiated cells in vertebrates are subject to turnover through cell death and renewal. In some cases, the fully differentiated cell simply divides to produce daughter cells of the same differentiated type. Hepatocytes in the liver and endothelial cells lining blood vessels are examples. The rate of proliferation of such cells is controlled to maintain appropriate total cell numbers. Thus if a large part of the liver is destroyed, the remaining hepatocytes increase their division rate to restore the loss. But repair is often imperfect, as when the fibroblasts in a severely damaged liver grow too rapidly in relation to the hepatocytes and replace them with fibrous tissue.

Endothelial cells form a single cell layer that lines all blood vessels and regulates exchanges between the bloodstream and the surrounding tissues. New blood vessels develop from the walls of existing small vessels by the outgrowth of these endothelial cells, which have the capacity to form hollow capillary tubes even when isolated in culture. In the living animal, damaged tissues and some tumors attract a blood supply by secreting factors that stimulate nearby endothelial cells to construct new capillary sprouts. Tumors that fail to attract a blood supply are severely limited in their growth.

Renewal by Stem Cells: Epidermis

From cell populations that are renewed by simple duplication, we turn now to those that are renewed by means of **stem cells.** These populations vary widely, not only in cell character and rate of turnover, but also in the geometry of the process of cell replacement. In the lining of the small intestine, for example, cells are arranged as a single-layered epithelium. This epithelium covers the surfaces of the *villi* that project into the lumen of the gut, and it lines the deep *crypts* that descend into the underlying connective tissue (Figure 16–20). The stem cells lie in a protected position in the depths of the crypts. The differentiated cells generated from them (see p. 614) are carried upward by a sliding movement of the epithelial sheet until they reach the exposed surfaces of the villi, from whose tips they are finally shed. A contrasting example is found in the skin: here the epidermis is a many-layered epi-

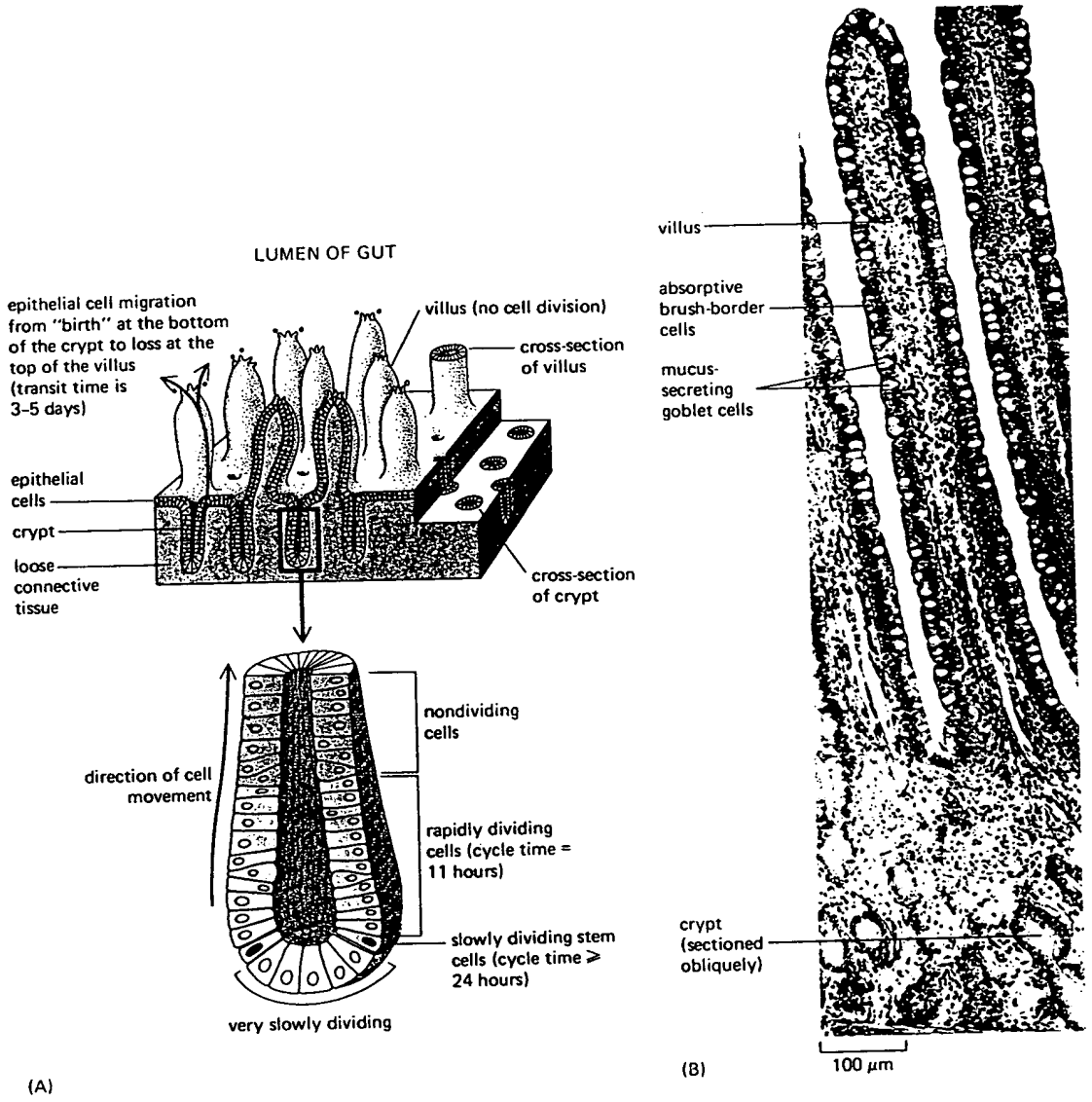

Figure 16–20 (A) Schematic diagram showing the pattern of cell turnover and the proliferation of stem cells in the lining of the small intestine. (B) Photograph of a section of part of the lining of the small intestine, showing the villi and crypts. Note how mucus-secreting goblet cells (visible as pale ovals) are interspersed among the absorptive brush-border cells in the epithelium of the villi. (Courtesy of Peter Gould.)

thelium, and the differentiating cells travel outward from their site of origin in a direction perpendicular to the plane of the cell sheet. In the case of blood cells, the spatial pattern of production appears chaotic. Before going further into such details, however, we must pause to consider what a stem cell is.

Stem Cells Have the Ability to Divide Without Limit and to Give Rise to Differentiated Progeny[17]

The defining properties of a stem cell are as follows:

1. It is not itself terminally differentiated (that is, it is not at the end of a pathway of differentiation).
2. It can divide without limit.
3. When it divides, each daughter has a choice: it can either remain a stem cell like its parent, or it can embark on a course leading irreversibly to terminal differentiation (Figure 16–21).

What factors determine whether stem cells exercise their ability to divide or stay quiescent? What governs the choice that a daughter cell must make between terminal differentiation and life as a stem cell? And what range of

possibilities does a daughter cell have when it embarks on a pathway leading to terminal differentiation? These are central questions to be considered in the following sections.

Stem cells are required wherever there is a recurring need to make new differentiated cells and the differentiated cells cannot themselves divide. In several tissues, the terminal state of cell differentiation is obviously incompatible with cell division. For example, the cell nucleus may disintegrate, as in the outermost layers of the skin, or be extruded, as in the case of mammalian red blood cells. Alternatively, the cytoplasm may be heavily encumbered with materials, such as the myofibrils of muscle cells, that would get in the way of mitosis and cytokinesis. In other terminally differentiated cells the chemistry of differentiation may be in some more subtle way incompatible with cell division. In any such case, renewal must depend on stem cells.

The job of the stem cell is not to carry out the differentiated function, but to produce cells that will. Consequently, stem cells often have a rather nondescript appearance, making them hard to identify. But that is not to say that stem cells are all alike. Though not overtly differentiated, they are nevertheless *determined* (see p. 835): the muscle satellite cell, as a source of skeletal muscle; the epidermal basal cell, as a source of keratinized epidermal cells; the spermatogonium, as a source of spermatozoa; the basal cell of olfactory epithelium, as a source of olfactory neurons (Figure 16–22); and so on. Those stem cells that give rise to only one type of differentiated cell are called *unipotent;* those that give rise to more than one type are called *pluripotent.* We begin our discussion with the **epidermis,** for its simple spatial organization makes it relatively easy to study the natural history of its stem cells and the fate of their progeny.

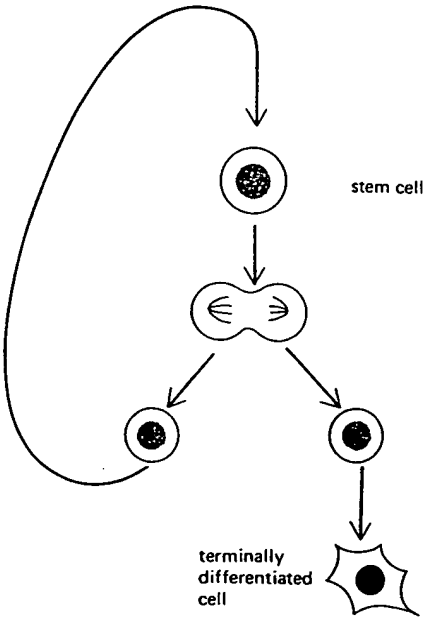

Figure 16–21 Each daughter produced when a stem cell divides can either remain a stem cell itself or go on to become terminally differentiated.

The Epidermis Is Organized into Proliferative Units[18,19]

The epidermal layer of the skin and the epithelial lining of the digestive tract are the two tissues that suffer the most direct and damaging encounters with the external world. In both, mature differentiated cells are rapidly lost from the most exposed positions and just as rapidly replaced by the proliferation of less differentiated cells that occupy more sheltered niches.

The epidermis comprises several layers that differ in appearance (Figure 16–23). The inner layers consist of metabolically active cells, strongly bound together by spot desmosome junctions; the cells of the outer layers are dead relics, packed full with the fibrous protein keratin. The innermost of the inner layers is composed of *basal cells* that sit on the basal lamina that separates the epidermis from the underlying dermis. It is chiefly these cells that undergo mitosis. Above the basal cells are several layers of larger, flatter *prickle cells.*

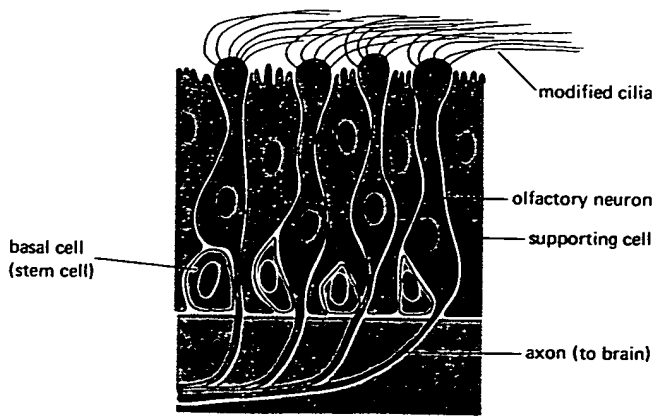

Figure 16–22 Schematic diagram of a section of olfactory epithelium (specialized for sensing smells). Three cell types can be distinguished: supporting cells, basal cells, and olfactory neurons. Autoradiographic experiments show that the basal cells are the stem cells for production of the olfactory neurons, which constitute one of the very few exceptions to the rule that neurons are permanent cells. Each olfactory neuron survives for about a month (in a mammal) before it is replaced. Six to eight modified cilia project from the globular head of the olfactory neuron and are believed to contain the smell receptors. The axon extending from the other end of the neuron conveys the message to the brain. A new axon must grow out and make appropriate connections whenever a basal cell differentiates into an olfactory neuron.